



Case Report

Methylene blue for the treatment of refractory anaphylaxis without hypotension[☆]

Abstract

Anaphylaxis is a life-threatening reaction treated primarily with epinephrine. Methylene blue, a competitive inhibitor of guanylate cyclase, interferes with the vasodilatory actions of nitric oxide. It has recently been proposed by the Joint Taskforce on Practice Parameters as an alternative treatment for anaphylaxis with hypotension that is not responsive to classical therapy. Little evidence supports its use in normotensive patients with refractory anaphylaxis. We present the case of a 43-year-old woman with severe anaphylaxis unresponsive to epinephrine. Physical examination revealed marked respiratory distress, raised oral lesions, and altered mental status but lacked hypotension. After infusion of methylene blue, symptom resolution occurred almost immediately, and intubation was spared. Side effects were minimal. We propose methylene blue as a safe treatment option for refractory anaphylaxis, whether with or without hypotension.

Anaphylaxis can occur after an immunoglobulin E-mediated reaction to food, drugs, insects, or other stimuli. It is termed *idiopathic* when the cause is unknown. The mainstay of treatment is epinephrine, followed by oxygen, fluids, antihistamines, inhaled β -agonists, and glucocorticosteroids. In cases of anaphylaxis “resistant” to epinephrine, alternatives must be used. We describe a case of refractory anaphylaxis without hypotension treated successfully with methylene blue.

A 43-year-old perimenopausal white woman with idiopathic anaphylaxis acutely developed oral papules, urticaria, and dyspnea at 11 AM while working at a school. She denied having anything to eat, although she had taken her usual medications, aspirin and citalopram, 4 hours earlier.

Her medical history included allergic rhinitis, peanut allergy, depression, cerebrovascular disease, and 6 recent episodes of anaphylaxis, all with identical features to the

current episode. In working up her anaphylaxis, baseline total tryptase was not elevated (2.32 ng/mL), bone marrow biopsy was negative for the D816V mutation, and urinary 5-hydroxyindoleacetic acid (5-HIAA), vanillylmandelic acid (VMA), and catecholamines were negative.

Because these prodromal symptoms were identical to prior episodes, she immediately administered epinephrine 0.3 mg by autoinjector. Within minutes, she developed a choking sensation. She administered a second dose of epinephrine 0.3 mg 10 minutes later, took oral diphenhydramine 50 mg, and called the paramedics. Ten minutes later, with persistent dyspnea, she administered a third dose of epinephrine 0.3 mg.

Upon paramedic arrival, she was given oxygen for respiratory distress. She was normotensive. A fourth dose of epinephrine 0.3 mg, diphenhydramine 60 mg IV, saline, and nebulized albuterol were given.

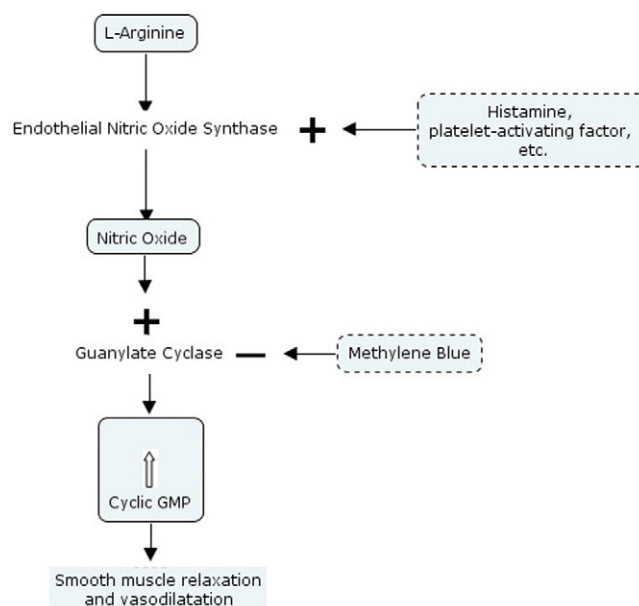


Fig. 1 Endothelial nitric oxide synthase converts L-arginine to nitric oxide, a reaction that is up-regulated in the presence of histamine and PAF. Nitric oxide increases the activation of guanylate cyclase, which then increases cyclic guanosine monophosphate (cyclic GMP). These events result in smooth muscle relaxation and vasodilation. + indicates up-regulates/activates; −, down-regulates/inhibits.

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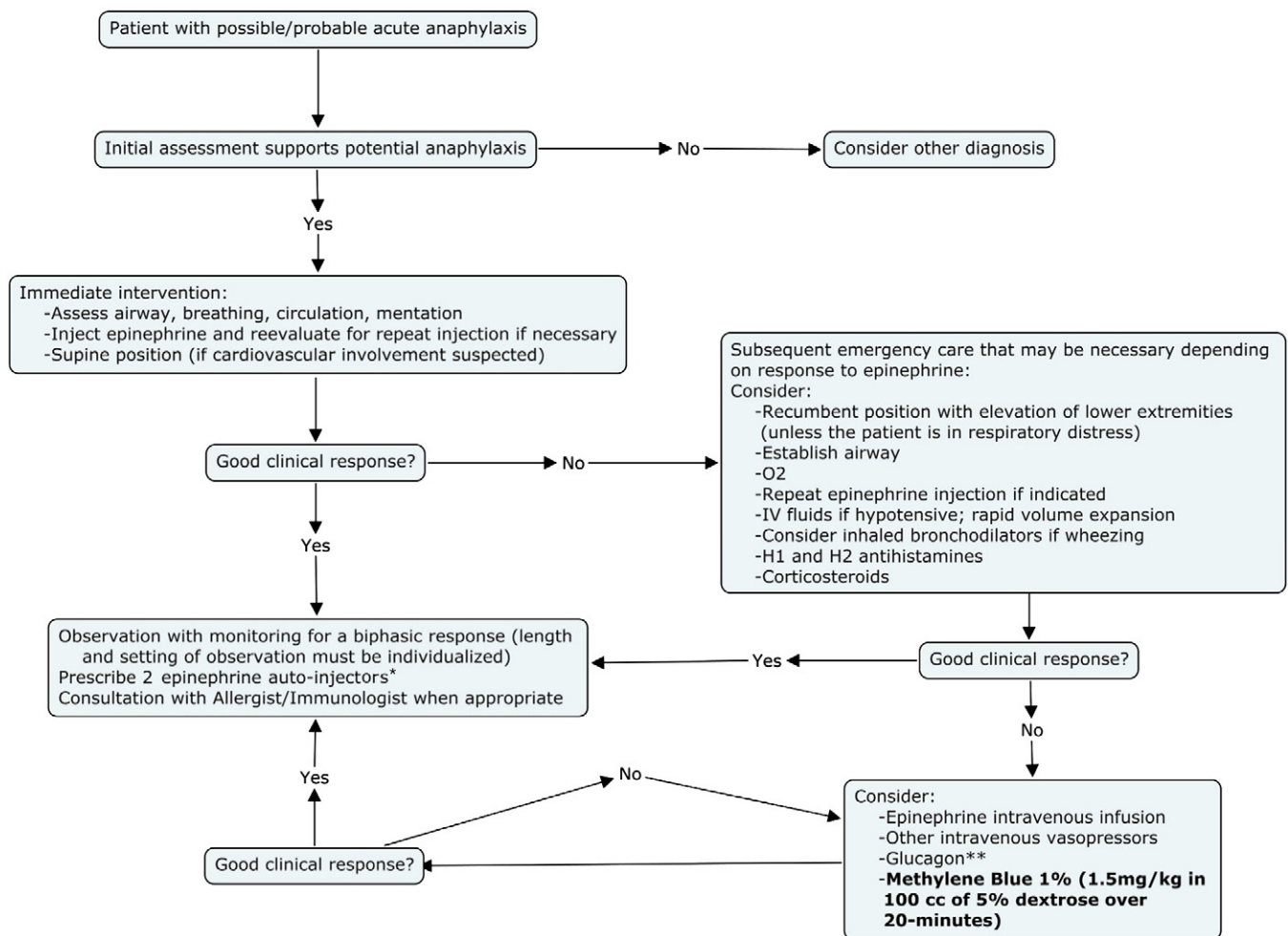


Fig. 2 Modified algorithm for the treatment of anaphylaxis [6]. Methylene blue is included as an alternative agent for cases refractory to epinephrine. *Because 16% to 36% of anaphylactic episodes require 2 epinephrine injections, 2 epinephrine autoinjectors should be prescribed [15]. **Glucagon activates adenyl cyclase directly and bypasses the β -adrenergic receptor; it has been recommended when epinephrine is ineffective in treating anaphylaxis in patients taking β -blockers [6,16].

In the emergency department, heart rate was 84 beats per minute; blood pressure, 170/90 mm Hg; respiratory rate, 16 breaths per minute; and oxygen saturation, 100% on a bag mask. Arterial blood gas was obtained but later clotted. Physical examination revealed depressed consciousness, prolonged expiration with diffuse wheezing, abnormal voice, and 5-mm erythematous oral papules. Urticaria, angioedema, and stridor were not noted. Direct laryngoscopy was not performed. Methylprednisolone 125 mg IV, famotidine 20 mg IV, and continuous nebulized albuterol were given. After 15 minutes, she failed to improve.

Infusion of methylene blue 1% was begun at 1.5 mg/kg in 100 mL of 5% dextrose. Six minutes into this 20-minute infusion, she became remarkably less dyspneic, and by 13 minutes, she was speaking clearly. Upon completion, she complained only of mild nausea.

Subsequent episodes of anaphylaxis correlated with her menstrual period, and catamenial anaphylaxis was diagnosed. Given her history of stroke, hormonal therapies were

contraindicated. She underwent elective hysterectomy/bilateral salpingo-oophorectomy with remission of anaphylaxis.

Methylene blue is used as an indicator dye and in treating methemoglobinemia, malaria, and chronic urolithiasis. In 1997, Evora [1] first proposed methylene blue for anaphylactic shock. He described 3 patients failing repeated doses of epinephrine. All had rapid reversal of their cardiovascular collapse with methylene blue. Although no controlled studies have been performed, additional case reports have been published [2-5]. Interestingly, there are few that describe the use of methylene blue in patients without hypotension [5]. In fact, the Joint Taskforce on Practice Parameters recommends methylene blue "if anaphylaxis is associated with hypotension" [6]. Our patient was not hypotensive yet responded dramatically to methylene blue.

Methylene blue is a competitive inhibitor of guanylate cyclase, preventing cyclic guanosine monophosphate-dependent smooth muscle relaxation and vasodilation (Fig. 1). This blocks downstream effects of nitric oxide, including mediators released upon mast cell degranulation, such as

histamine and platelet-activating factor (PAF) [7-9]. PAF is a potent mediator of anaphylaxis [10], presumably through binding a G protein-coupled 7-transmembrane receptor, the PAF receptor [11]. In mice, treatment of peanut-induced anaphylaxis with PAF blockers reduced severity of anaphylaxis [12]. Levels of PAF are controlled by PAF-acetylhydrolase (PAF-AH). In humans, serum PAF levels have been shown to correlate directly with the severity of anaphylaxis, whereas PAF-AH levels correlated inversely. A deficiency of PAF-AH has been proposed to be an independent risk factor for fatal anaphylaxis [10].

Although nitric oxide synthase inhibitors attenuate hypotension and hemoconcentration and decrease venous return, they do not improve cardiac output and may increase risk for tissue necrosis and bronchospasm. This is not seen with methylene blue because it does not block nitric oxide production [8,13].

Side effects of methylene blue are minimal. Nausea, vomiting, abdominal pain, fever, hemolysis, hypotension, methemoglobinemia, arrhythmias, bluish skin, urine discoloration, and hyperbilirubinemia have been described [8]. At the low dose used for anaphylaxis (1.5-2.0 mg/kg), side effects are few. In anaphylaxis, it is important to remember that methylene blue interferes with pulse oximetry, causing factitious oxygen desaturation [14]. In most cases, response to methylene blue is rapid, with clinical response within 20 minutes [8]. Our patient improved within 13 minutes.

Because anaphylaxis is potentially fatal, treatment alternatives for cases refractory to epinephrine are essential. Methylene blue has been shown to be a life-saving option with few adverse effects [3,8]. It should be considered a safe and effective option for patients, with or without hypotension, whose anaphylactic reactions are not responsive to epinephrine (Fig. 2).

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